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SHORT REPORT

Ischaemic colitis associated with intravitreal administration of aflibercept: A first case report

Benjamin Batteux[1] | Valérie Gras[1] | Yanis Mahboud[1] | Sophie Liabeuf[1,3] | Youssef Bennis[2,3] | Kamel Masmoudi[1]

[1] Centre Régional de Pharmacovigilance, Service de Pharmacologie Clinique, CHU Amiens-Picardie, Amiens, France

[2] Laboratoire de Pharmacologie, Service de Pharmacologie Clinique, CHU Amiens-Picardie, Amiens, France

[3] INSERM U 1088, Université de Picardie Jules Verne, Amiens, France

Correspondence
Benjamin Batteux, Service de Pharmacologie Clinique, Centre Régional de Pharmacovigilance, Centre de Biologie Humaine, F-80054 Amiens, France.
Email: batteux.benjamin@chu-amiens.fr

In patients with age-related macular degeneration (AMD), the intravitreal injection of antivascular endothelial growth factor (anti-VEGF) agents reduces disease progression and choroidal neovascularization. We report on a first case of ischaemic colitis associated with intravitreal injection of the anti-VEGF agent aflibercept in an 80-year-old female patient. Conservative treatment resulted in a favourable clinical outcome. The anti-VEGF agent was discontinued, and the symptoms did not recur. Although the intravitreal injection of anti-VEGF agents has not previously been linked to the occurrence of ischaemic colitis, consideration of aflibercept's pharmacological properties and the chronological relationship between the administration of this anti-VEGF agent and the occurrence of this systemic adverse event are strongly suggestive of a causal relationship in the present case. Although systemic complications have been rarely associated with intravitreal injections of anti-VEGF agents, physicians should be aware that novel adverse events can still occur in AMD patients treated with anti-VEGF agents.

KEYWORDS

adverse effect, intravitreal aflibercept, ischaemic colitis, pharmacovigilance

1 | INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of visual impairment and blindness in elderly populations.[1] Vascular endothelial growth factor (VEGF) has emerged as a key therapeutic target, and intravitreal injections of anti-VEGF agents (eg **bevacizumab**, **ranibizumab** and **aflibercept**) are now widely employed to reduce disease progression and choroidal neovascularization in patients with AMD. However, intravitreal injections may be responsible for complications; although these are predominantly local (eg intraocular inflammation or infections, endophthalmitis, elevated intraocular pressure, retinal detachment and vitreous haemorrhages), systemic events (eg thrombotic events, myocardial infarction, stroke, hypertension and gastrointestinal perforation) have been described.[2-4]

Here, we report on the first case of ischaemic colitis associated with intravitreal injection of aflibercept, as reported spontaneously to the French National Pharmacovigilance Network.

1.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.[5]

2 | RESULTS – CASE PRESENTATION

An 80-year-old woman with arterial hypertension and dyslipidaemia had been treated with **olmesartan** (20 mg/day), **spironolactone** (25 mg/day), altizide (15 mg/day) and **pravastatin** (20 mg/day) for several years. She had developed deep vein thrombosis a few years previously, although no predisposing factors had been identified. The hypertension was well controlled by her medications, and no episodes of hypotension had been observed. The patient did not present with any other cardiovascular risk factors, kidney disease, cancer, malignant blood disease or vasculitis.

In December 2015, the woman underwent bilateral cataract surgery. Treatment for AMD (3-monthly intravitreal injections of 2 mg aflibercept in a volume of 50 μL, in each eye) was initiated in January 2016, after discovery of bilateral AMD.

In the days following the first bilateral intravitreal injection, the patient experienced malaise (without loss of consciousness) and floaters. The same symptoms occurred after the second injection (on 6 February 2016). The patient was hospitalized 3 days later because of the occurrence of acute abdominal pain and rectal bleeding. There were no signs of dehydration, and the patient's renal function (creatinine clearance) was stable relative to the rate of 70 ml/min recorded in 2014. The patient's blood pressure was normal, and there were no signs of infection. A computed tomography scan of the abdomen revealed left-sided ischaemic colitis (Figures 1 and 2). A colonoscopy performed on 22 February 2016 confirmed the diagnosis of ischaemic colitis, and highlighted an erosive mucosa. A biopsy showed that the chorionic mucosa was inflamed and oedematous.

The patient's cardiac status (as assessed with an electrocardiogram, transthoracic echocardiography and Holter monitoring) was normal, as was her haematological status (with no signs of polycythaemia, in particular). Conservative treatment (bed rest, nil by mouth and intravenous hydration) led to a favourable clinical outcome. The last of the three planned injections was not performed. At last follow-up (23 May 2017), the symptoms had not recurred.

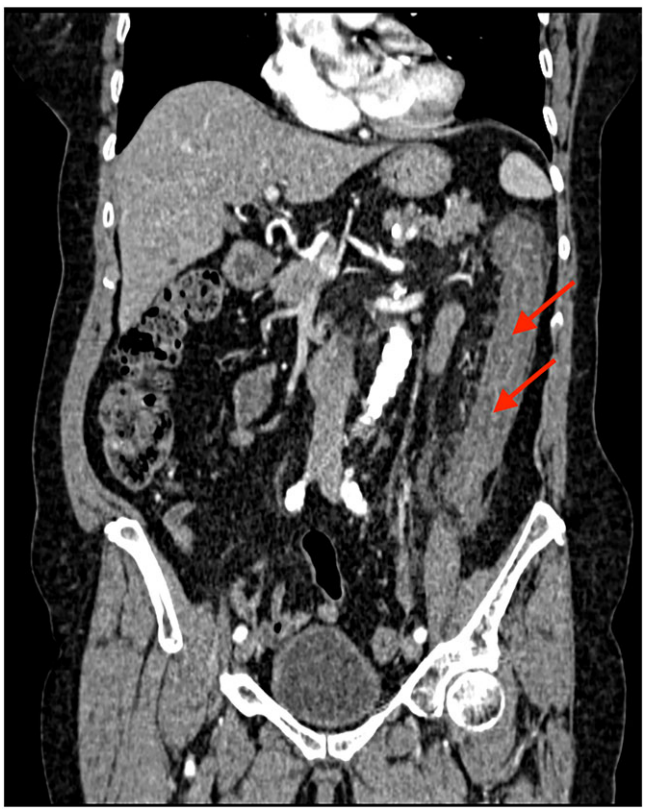

FIGURE 1 Computed tomography image showing ischaemic colitis of the left colon (lateral view). Red arrows: thickening of the colonic wall and infiltration of the mesenteric fat

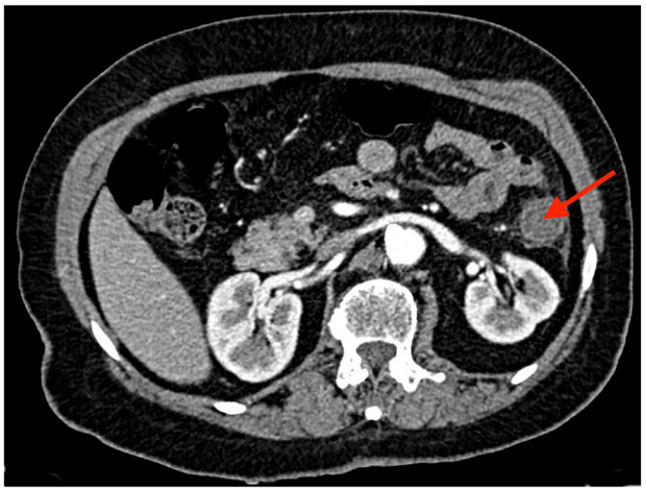

FIGURE 2 Computed tomography image showing ischaemic colitis of the left colon (transverse view). Red arrow: thickening of the colonic wall and infiltration of the mesenteric fat

3 | DISCUSSION

In the present case, we observed a close chronological relationship between the intravitreal injections of aflibercept and the occurrence of malaise and ischaemic colitis. Furthermore, the adverse event did not recur after the discontinuation of aflibercept. The fact that the patient had been taking other medications (olmesartan, spironolactone, altizide and pravastatin) for a long time before the adverse events occurred (and continued to take them after the event had resolved) indicates that the said medications were probably not responsible. None of the concomitant medications are known to induce ischaemic colitis, and no potentially related aetiological factors were identified after appropriate in-hospital assessments. According to the Naranjo adverse reaction probability scale score, aflibercept-induced ischaemic colitis was probable.[6]

The recently developed anti-VEGF agent, aflibercept, is indicated in the treatment of AMD. This human recombinant fusion protein binds to **placental growth factor** and all isoforms of **VEGF-A** and **VEGF-B**.

When administered intravenously in the context of metastatic colorectal cancer, anti-VEGF agents have been linked to an elevated incidence of arterial thromboembolic events (including transient ischaemic attack, stroke, intracardiac thrombus, myocardial infarction and arterial embolism) and venous thromboembolic events (including deep vein thrombosis and pulmonary embolism).[7] The summary of product characteristics (SmPC) for aflibercept[8] mentions the possible occurrence of arterial thromboembolic events following intravitreal injection.[2,3] Logically, the SmPC mentions that simultaneous bilateral administration can lead to increased systemic exposure and is likely to increase the risk of systemic adverse events.[7]

The present report describes the first case of ischaemic colitis associated with the intravitreal administration of an anti-VEGF agent to have been recorded in the French national pharmacovigilance database. However, three other cases of ischaemic colitis after intravitreal aflibercept injection have been reported in Vigibase, the World Health Organization global pharmacovigilance database

(date of access: 24 August 2018)[9]: two cases from Japan (a 68-year-old man and an 83-year-old man, the latter died) and a case from Australia (a 91-year-old man).

Moreover, this adverse event is rarely described in the literature. Onoda et al. reported one case of ischaemic colitis after intravitreal injections of bevacizumab.[10] No other publications have mentioned the occurrence of this adverse effect after the injection of aflibercept or ranibizumab.

The role of anti-VEGF agents in the development of systemic adverse events remains unclear. The events described after inhibition of VEGF (such as bleeding and thrombosis) reflect this factor's many essential functions with regard to the vessel walls and components of the coagulation system. Most of these effects appear to be due to VEGF's ability to induce the production of nitric oxide and prostaglandin I_2, both of which are responsible for the majority of the growth factor's vascular effects (ie vasodilatation and the increased survival, proliferation and migration of endothelial cells). Indeed, inhibition of VEGF might decrease the endothelial cells' regenerative capacity, provoke defects that expose procoagulant phospholipids on the vessel wall, and thus predispose to thromboembolic events.[11] Furthermore, anti-VEGF agents may also increase the risk of thrombosis by elevating the haematocrit and blood viscosity via the overproduction of erythropoietin.[12]

Intravitreal injection is likely to produce detectable levels of anti-VEGF agent in the systemic circulation. The resulting neutralization of systemic VEGF provides a scientific rationale for the occurrence of systemic adverse events.[13,14] The relationship between the thromboembolic risk and concentration of anti-VEGF agent explains why the frequency of systemic adverse events is lower for intravitreal injection than for intravenous administration. However, systemic thromboembolic events after the intravitreal injection of an anti-VEGF agent are nevertheless possible.[3]

It has been suggested that the frequency of systemic adverse effects after intravitreal injection in AMD patients is higher for bevacizumab than for ranibizumab,[15] and that the systemic diffusion is more widespread for bevacizumab.[16] Recently, Avery et al.[17] highlighted notable differences between anti-VEGF agents with regard to their systemic pharmacokinetics and pharmacodynamics after the intravitreal injection of a standard dose. Although all the agents rapidly moved into the bloodstream, bevacizumab and aflibercept resulted in greater systemic exposure and a marked reduction in the plasma-free VEGF concentration, relative to ranibizumab.[17] Furthermore, the binding affinity of aflibercept for VEGF is greater than that of the other anti-VEGF agents used in the treatment of AMD; hence, stronger blocking of VEGF (even at low aflibercept concentrations) might translate into a longer duration of action and a higher risk of systemic side effects.[17]

In the case reported here, recent cataract surgery and possible injury to the eye-blood barrier (which is often damaged in neovascular disease) might have facilitated the release of aflibercept into the systemic circulation,[2] especially as aflibercept was administrated bilaterally simultaneously.[8]

Furthermore, cardiovascular risk factors may accentuate the risk of adverse events associated with anti-VEGF agents. For example, the incidence of stroke is higher in patients who have previously had a stroke.[18,19] However, patients with major cardiovascular disease or risk factors were often excluded from clinical trials of anti-VEGF agents; hence, one can expect to observe previously unreported adverse events in postmarketing studies of a broader population of patients with AMD.

Another key point is that, although AMD has been linked to a higher risk of stroke,[20] patients with AMD are usually elderly (ie where the risk of cardiovascular events is highest).

Lastly, in the present report, we cannot exclude the possibility that factors other than aflibercept contributed to ischaemic colitis, such as advanced age, the AMD itself and the patient's history of cardiovascular disease (hypertension and deep vein thromboembolism).

4 | CONCLUSION

The occurrence of ischaemic colitis has rarely been reported following the intravitreal injection of an anti-VEGF agent. However, in the present case, the chronology of the adverse event, the absence of an alternative aetiology, and the pharmacological properties of aflibercept are suggestive of a probable causal relationship. The report is thus the first to describe a case of ischaemic colitis that probably resulted from the intravitreal injection of aflibercept. Although intravitreal injections of anti-VEGF agents are rarely associated with systemic complications, patients with AMD (especially those with cardiovascular risk factors and those receiving several injections) should be carefully monitored, and the treatment should be discontinued rapidly if potentially linked adverse events occur.

COMPETING INTERESTS

There are no competing interests to declare.

CONTRIBUTORS

V.G., B.B. and Y.M. helped to draft the manuscript and interpret the data. S.L., Y.B. and K.M. helped to revise the article critically for important intellectual content.

ORCID

Benjamin Batteux https://orcid.org/0000-0001-9466-7110
Sophie Liabeuf https://orcid.org/0000-0001-5384-9006

REFERENCES

1. Chopdar A, Chakravarthy U, Verma D. Age related macular degeneration. *BMJ*. 2003;326(7387):485-488.
2. Costagliola C, Agnifili L, Arcidiacono B, et al. Systemic thromboembolic adverse events in patients treated with intravitreal anti-VEGF drugs for neovascular age-related macular degeneration. *Expert Opin Biol Ther*. 2012;12(10):1299-1313.
3. Falavarjani KG, Nguyen QD. Adverse events and complications associated with intravitreal injection of anti-VEGF agents: a review of literature. *Eye (Lond)*. 2013;27(7):787-794.
4. Cutroneo PM, Giardina C, Ientile V, et al. Overview of the safety of anti-VEGF drugs: analysis of the Italian spontaneous reporting system. *Drug Saf*. 2017;40(11):1131-1140.
5. Harding SD, Sharman JL, Faccenda E, et al. The IUPHAR/BPS guide to PHARMACOLOGY in 2018: updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucl Acids Res*. 2018;46(D1):D1091-D1106.

6. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.
7. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99(16):1232-1239.
8. European Medicines Agency. Eylea. INN: Aflibercept. https://www.ema.europa.eu/documents/product-information/eylea-epar-product-information_en.pdf. 2017. Accessed August 27, 2018.
9. Lindquist M. VigiBase, the WHO global ICSR database system: basic facts. *Drug Inf J*. 2008;42(5):409-419.
10. Onoda Y, Shiba T, Hori Y, Maeno T, Takahashi M. Two cases of acute abdomen after an intravitreal injection of bevacizumab. *Case Rep Ophthalmol*. 2015;6(1):110-114.
11. Zachary I. Signaling mechanisms mediating vascular protective actions of vascular endothelial growth factor. *Am J Physiol Cell Physiol*. 2001;280(6):C1375-C1386.
12. Tam BYY, Wei K, Rudge JS, et al. VEGF modulates erythropoiesis through regulation of adult hepatic erythropoietin synthesis. *Nat Med*. 2006;12(7):793-800.
13. Csaky K, Do DV. Safety implications of vascular endothelial growth factor blockade for subjects receiving intravitreal anti-vascular endothelial growth factor therapies. *Am J Ophthalmol*. 2009;148(5):647-656.
14. Matsuyama K, Ogata N, Matsuoka M, Wada M, Takahashi K, Nishimura T. Plasma levels of vascular endothelial growth factor and pigment epithelium-derived factor before and after intravitreal injection of bevacizumab. *Br J Ophthalmol*. 2010;94(9):1215-1218.
15. CATT Research Group, Martin DF, Maguire MG, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364(20):1897-1908.
16. Lim LS, Cheung CMG, Mitchell P, Wong TY. Emerging evidence concerning systemic safety of anti-VEGF agents—should ophthalmologists be concerned? *Am J Ophthalmol*. 2011;152(3):329-331.
17. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics following intravitreal injections of ranibizumab, bevacizumab or aflibercept in patients with neovascular AMD. *Br J Ophthalmol*. 2014;98(12):1636-1641.
18. Ciulla TA, Rosenfeld PJ. Antivascular endothelial growth factor therapy for neovascular age-related macular degeneration. *Curr Opin Ophthalmol*. 2009;20(3):158-165.
19. Mitchell P, Korobelnik J-F, Lanzetta P, et al. Ranibizumab (Lucentis) in neovascular age-related macular degeneration: evidence from clinical trials. *Br J Ophthalmol*. 2010;94(1):2-13.
20. Alexander SL, Linde-Zwirble WT, Werther W, et al. Annual rates of arterial thromboembolic events in Medicare neovascular age-related macular degeneration patients. *Ophthalmology*. 2007;114(12):2174-2178.

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